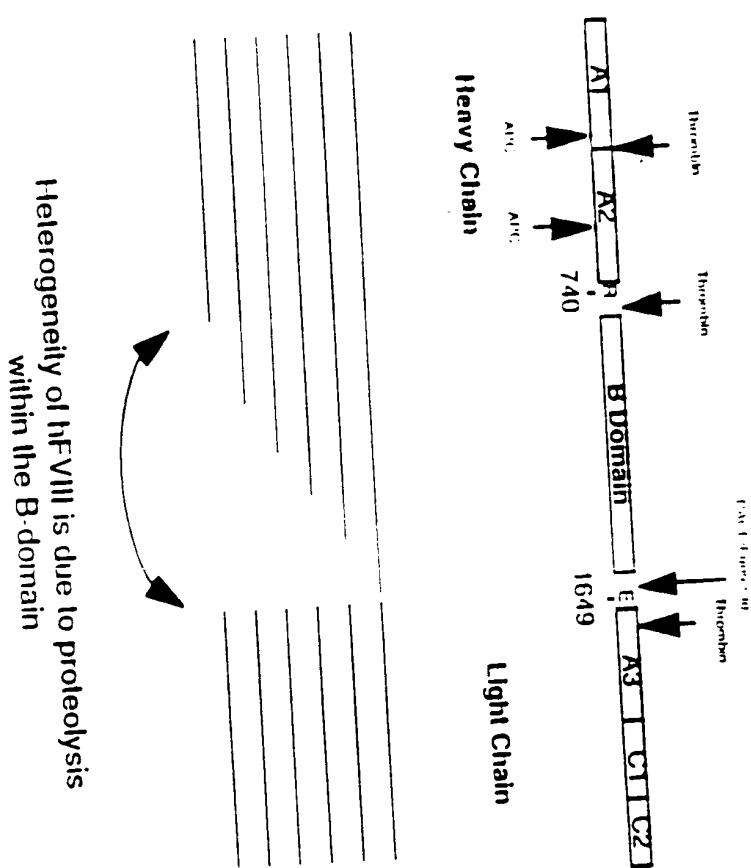
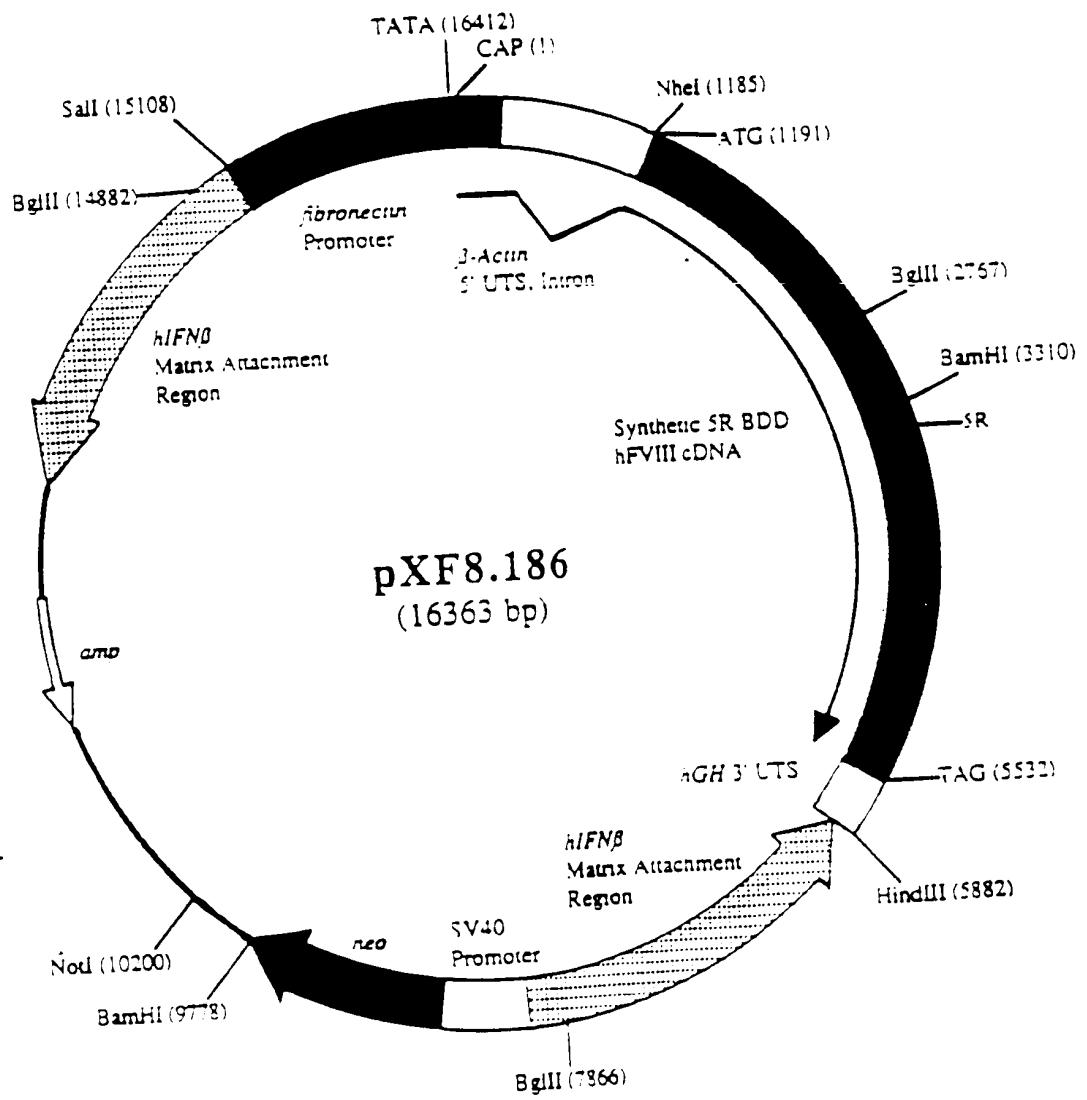


FIG. 1



Heterogeneity of hFVIII is due to proteolysis within the B-domain

FIG. 2



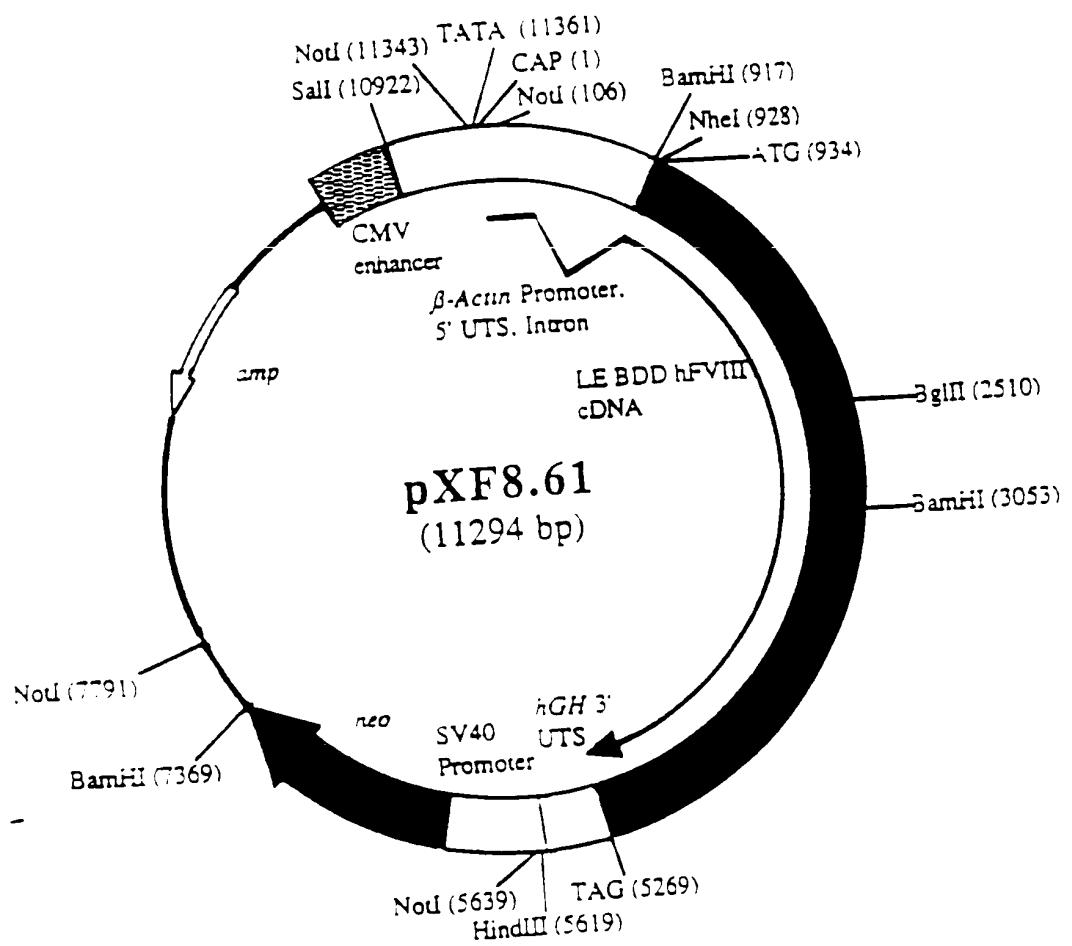


FIG. 4

Fragment A

AM1 AM1

5'-CTGAGAAATTCGTTAGCCCTAGCATCCAGATCCGAGCTGAGCACCTGCTTCTTCTGCTGCTCTGCTGCGCTCTGC
-3'

3.045 P

AM1 Ar2

3.0H 5`P
AM1 A13 31304

GG"GTCAAGAGAC CCTGTTGCGGAGTTACCGGACACCTGTTCAACATGGCAAGCCCCCCCC

CTGGATGGCCCTGCTGGCCCT\,CAGCTTTAC
Apal 141001

GGCTTACCCGGACGGCCGGTAAAGTTGGAATG

FIG. 5 (1 of 14)

Fragment B

AM1 Bl 1

Eco **II** **Apa** **I**
GTAGAATTCTGTAGGGCCCCACCATCAGGCCGAGGTGTACGACACCGTGGTGTACCTGAAGAACATGGCAG
CTCTTAAAGCTCCCCGGGTGCTAGCTCCGCCTCCACATGCTGTGGCACCACTAGTGGACTTCTTGTACCGGTC
AM1 Br3

3' OH 5' P

CCACCCCGTGAGC~T'GCCACGCCGTGGCGGTGAGCTACTG GAAGGCCAGGGCAAGGCCGGAGTAGGACCGACCAAGA
GTTGGGGCACTCG GACGTGC'~T'GCCACTCGATGAC CTTCCGGTCCGTCAT'CTTCCTGCTT
AM1 Br2

3' OH 5' P

AM1 Bl 2
CCAGCCAGCGCGAGAAGGGGACGACAAGGGTGTCCCCGG~CGGAGCCACACCTACGGTGTGGAGGTG
GGTCGGTCCGCTCTCCTCC'GGCTTCCACAAAGGGCC GCGTCGGTGTGGATGCCACACCGTCCAC_GACTTC
5' P 3' OH

AM1 Bl 3

Pml **I** **Hind** **III**
GAGAACCGCCCCATGGCCAGGCCACCCCTGTGCTGTACAGCTACCTGAGCCACGGTGTACAAAGCTTIA
CTCTTGCCGGGTAACCGGTGGCTGGGGACTGGATGTGATGGACTCGGTGACCGATGTCGAATG
AM1 Br1

FIG. 5 (2 of 14)

Fragment C

AM1 Cl 1

EcoRI PmlI
GTTAGAATTCGTTAGCCACGGTGGACCTGGTGAAGGACCTGAAACAGCGGCCTGATCGGGCCCTGGTGGCGAGGGCAGCCCTG
CATCTTAAAGCATCGGTGCACCTGGACCCACTTCCTGGACTTGTCCGGGACTAGCCGGGAGGACACAGGGCCTG

AM1 Cr 3

3' OH 5' P
GCCAGGGAGAGAC TGCAGACCCCTGCACAACTTCATC CTGCTGTGCCGTGTCGACGGAGGCAAGAGCCCTGGACAGCGAGACC
GGCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGAC
5' P 3' OH

3' OH 5' P
AGAAACAGCTGTAGCAGGAGCCGGACGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCC
TGTCTTCTGGACTACGGCTCTGGACCTGGCTGGGGGG CGCGGACCGGGTCTACCTGGACCTGGACCTGGACCTGGAC
5' P 3' OH

AM1 Cl 2

PmlI HindIII
AGCCCTGGCTGGCTGGCTGCCACCGCAAGAGCGTGTACTGGCACGGTGTACAGCTGGACCTGGACCTGGACCTGGACCTGG
TGTCTTCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGACCTGGAC

AM1 Cr 2

AM1 Cl 3
AM1 Cr 1

FIG. 5 (3 of 14)

Fragment D

AM 1 D 11

AM 104

AMID2

3' OH 5' P
 CCAGGC
 |
 CAGCCTGGAGATCCAGCCCCATCACCTTCTTGACCCCTGCTGATGGACCTGGCCAGACCTGGCTCTGCTGTTCTGGCCACATCA
 GAGGACAA
 |
 GACGGTGTAGT
 GCGCCG_GTCG_GAGGCTCTAGTCGGGGTAGGGAGGACTACCTGAGGAGGACAA
 5' P 3' OH
 AM1D_r3

AMID

GGAGCTGC

3' OH 5' P
 GCAGCCACCGAGCAC
 |
 GACGGCATGGAGGCCATGAGTGGACAGCTGGCCAGCTGGCATGAAGAACACGGAGGAGS⁷⁶
 GTCCTGGCTACCTCCGGATGCCACTTCC⁸³CTGTCGACGGGCTCCTCGGAGTGGACGCGTACTTCTTGTTGCTCC⁹⁰
 GTCCTGGCTACCTCCGGATGCCACTTCC⁹⁷CTGTCGACGGGCTCCTCGGAGTGGACGCGTACTTCTTGTTGCTCC¹⁰⁴
 5' P 3' OH

AM 1 Dr 2

240

By III
Bank III

CCGACAACT

۱۰۷

111

CCTACAAAGCTTAC
GGAATGTTTCGAAATG

FIG. 5 (4 of 14)

Fragment F

AM1 Fr1

HindIII **KpnI**
GTAAGCTGTAGGGTACCGAGCTGGGTTCGGTCAACACGCTGAACAGGGATCACGTTCGCTGCAGCGCTCCATGGTCGACGCCAAGAGCAGCTGTGCGACTGTGCTCATGATCTGGTIGCC
5' P 3' OH
AM1 Fr3

AM1 Fr2

3' OH 5' P
G CGCTGGTCCACGCCCTCTCTGTAGCAGAAGCAGCAGGGGGGATCAGGGCGCTGGCCAGGTGGCTCCATGTCACGAAGCTG
C CGGAGCCAGGTGCCAGAGGAGCATCGTCCTAGTCCGGGACCGGTTGGCGAGGTTACAAGTG
AM1 Fr2

AM1 Fr3

BglII
3' OH 5' P
CTGTAGTAGGGGGTCAG GCAGGGGGGGCTCTCTGGGGCCGCTCCACGGCACCGGTCAC
GACATGTCGGCCAGTC CGTCGCCCAAGCAGAACACCCGGCAGGGTGCCTGAGCTTGAGAGCTG
AM1 Fr1

EcoRI
GAATTCCTAC
CTTAAAGATTC

FIG. 5 (6 of 14)

Fragment G

AMIGI

EcoRI **KpnI** **AM1Gr1**
GTAGAATTTCGTAGGGTACCTGACCGAGAACATCCAGCGCTTCTGCCA
CCCCGGGGGTTGCGAGCTGGAGGCCGAGTCAGGCCAG
GTAGCTTCTGGCTCTGCGGAAGGACGGGTGGGGCGCCCTTCGACCTCTGGGCTTC
AM1Gr3
AM1Gr2

AVIATION

3-OH-5-D

AM1G12
TGCACGGAGG1GCC1ACTGGTACATCCTGAG
ACCTGCTGCTACGGGATGACCTGTAGGCTC
AM1G2

5' P 3' OH 3' OH 5' P
 CATCGGGCCAGACCGACTTCCTGAGCGTGTTCTCAGC~GGCTACACTTCAGCACAGAGTGTGTTGAGGACTTCGCACTAGTCG
 GTAGCCCCGGGTCTGGCTGAAGGAGTTCGTGTTAC_~CACAGTGCCTGTTGGACCTGGTGTGTTAGTCG
 5' P 3' OH

BamH1 HindIII

AM1G|3

CCCCCTTCAGCCTGGAGACCGGTTCTATGAGCTTGGAGAACCCGGCTGGATCCCTACAAAGCTTAC
GGGAGAAGTCCGCGCTCTGGCACAGTACTCTGAACTCTTGGGGCGGACACCTAGGGATGTTGAAATG
AM1Gr1

AM
11

FIG. 5 (7 of 14)

Fragment H

AM 1 Hf 1

AM 1 H 12

AM 1113

111

3 OH 5' P
 CCCAGAAGAAGACC CGCCACTACTCATGCCCGCGCTGGGGACTACGGCATGAGCAGCCCCCACGTGCTACAAGCTTAC
 AGCTCTTCCTCTGG GCGGGTGTGAGMTAGGGGGGAGCTCGGGGACACCCCTGATGCCGTACTCGTGTGGAAATG
ΔM1H1

111

AM1H14 β_m 1 min

5'-CACGGTGTACAAAGC-3'

FIG. 5 (8 of 14)

Fragment I

AM1111
-TTAGGGGGGGAG~CTTCACCA(

ECMII PmII
 TCGGGGACCTGGCTGGCAACCGGGCCAGAGCTGCGGTTGCCAGGAGTCAGGCTGGCGTTCAGGGAGTCACGGCGT
 GAGGCTGGCTGGCGTGGCTGGCGTGGCTGGCGTGGCTGGCGTGGCTGGCGTGGCTGGCGTGGCTGGCGTGGCGT
 5' P 3' OH

Apal

AMI 112

BstEII
TGGGACCGGTGCAGGAGTCG
ACCACTGGCCAGGCTTCAGG
5 p

AM113
AMERICAN ECONOMIC ASSOCIATION

3' OH 5' P
 GAGACCAAGAGCTTGGGTTTCACCC
 GAGACCAAGAGCTTGGGTTTCACCC

AM 1 hr 2
STEREOTYPIC LEGACIES; ANARCHIST STRUGGLE

3 O¹ 5 P

5' TCAAGGAGAAC TACCGCTTCCACG
3' CCATCAACGGCTTACAGCACTGGC
5' TCGGCGGGTGC _GGTAGTGTGGCGATGTTGACG
3' **ATTCAT**

GENTILE

FIG. 5 (9 of 14)

Fragment J

AM1J11
GCAGCCCTGATCAGCTACGAGGAGCCAGCGCC

MIMO

AM1Jt2
TATGGCCCC

3' OH 5' P
AGG~GCG~CGAGCCCCGCAAGAACTTC GGTGAAGCCCAACGAGACCAAGACCTACTCTGGAA
TCCG CGGGGCTCGGGCGTTCTTGAGC GATTTGGGTTGCTCTGGTTCTGGATGAA;CCTTTCACGTGCTGGTACCCGTTTGGT
5' P 3' OH
AM1 Jr2
3' OH 5' P
GGAGCAGGAGTTCGACTGCAAGGCCCTGGGCTTACACTTCCAG~CGACGTGGACCTGGAGAAGGAC GGTGCA
CCTGCTCAAGCTGACCGTTCCGGACCCGGATGAGTC GCTGCACCTGGACCTCTCCCTG GACGTGTCGGCGACTAGCCGGGGAGGAC
5' P 3' OH

FIG. 5 (10 of 14)

Fragment K

AMIKI

P
111

AM1K13

APPLIED

FIG. 5 (11 of 14)

Fragment L

AM 111

3. OH 5. P 5. H 3. OH

AM1L[3] SmaI HindIII

AMILI

FIG. 5 (12 of 14)

Fragment M

I AM MY OWN MAN

GTAGAAATTCTGAGGATATCATCGCCCCGC1ACAC1CCCGCCGCGGCGGACCTGGGGTGGGGTGTGCGTACAGGCGGTCGTTGGGACGGG

TCAGCTTGCGAGCTGGCATGGCCCCCTGG GCATGGAGAGCAAGGCCATCAGGAACTCCAGGAA

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CCCCCTTCTTACGGTGGACTTCCAGAAGACCCATGAAGGTGACCTTACAAAGCTTAC

THE RECOGNITION OF ANGELA

FIG. 5 (13 of 14)

Fragment N

AMIN 1

AMIN3

AM1Nr1

Линд

FIG. 5 (14 of 14)

1

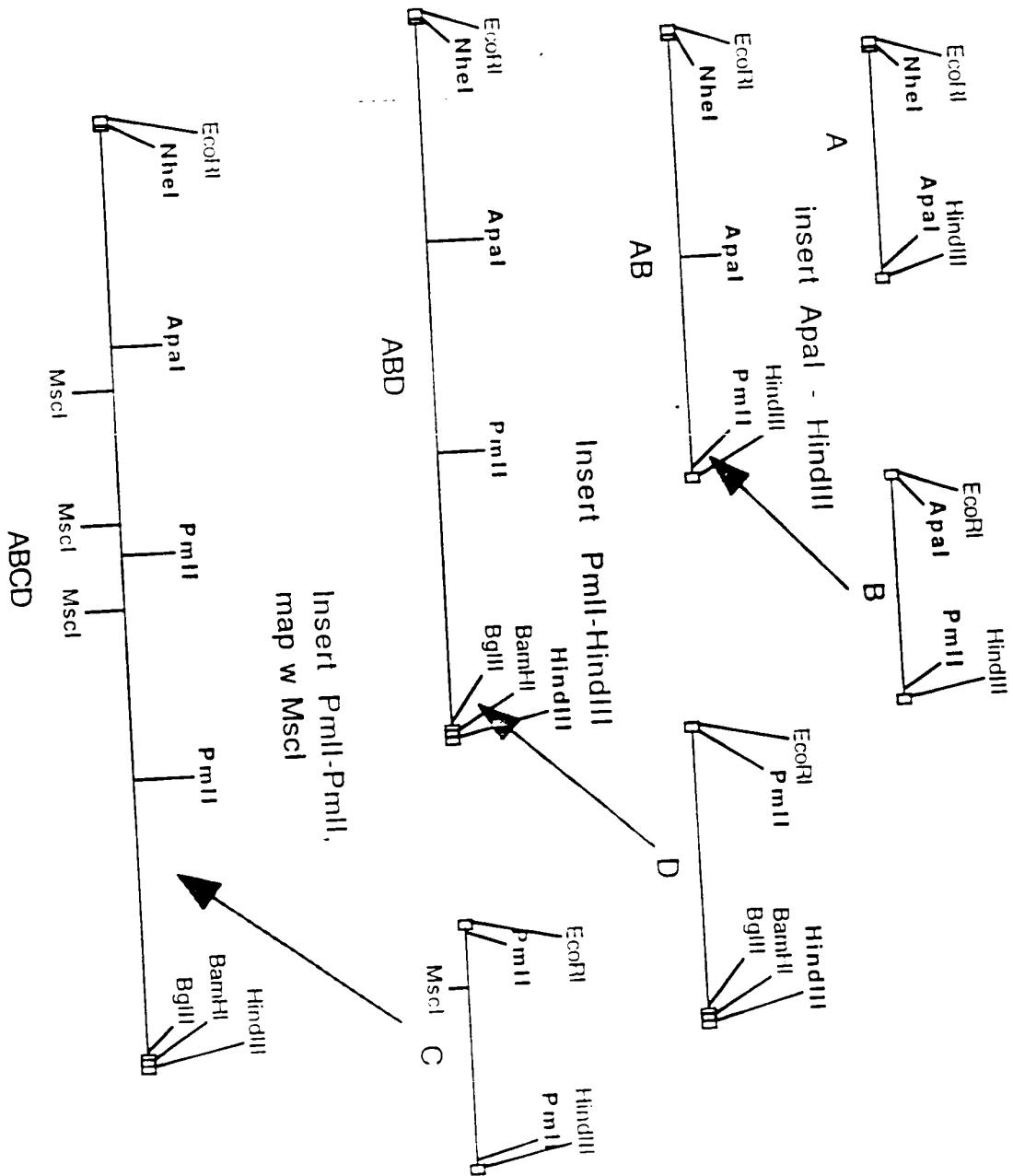


FIG. 6 (1 of 5)

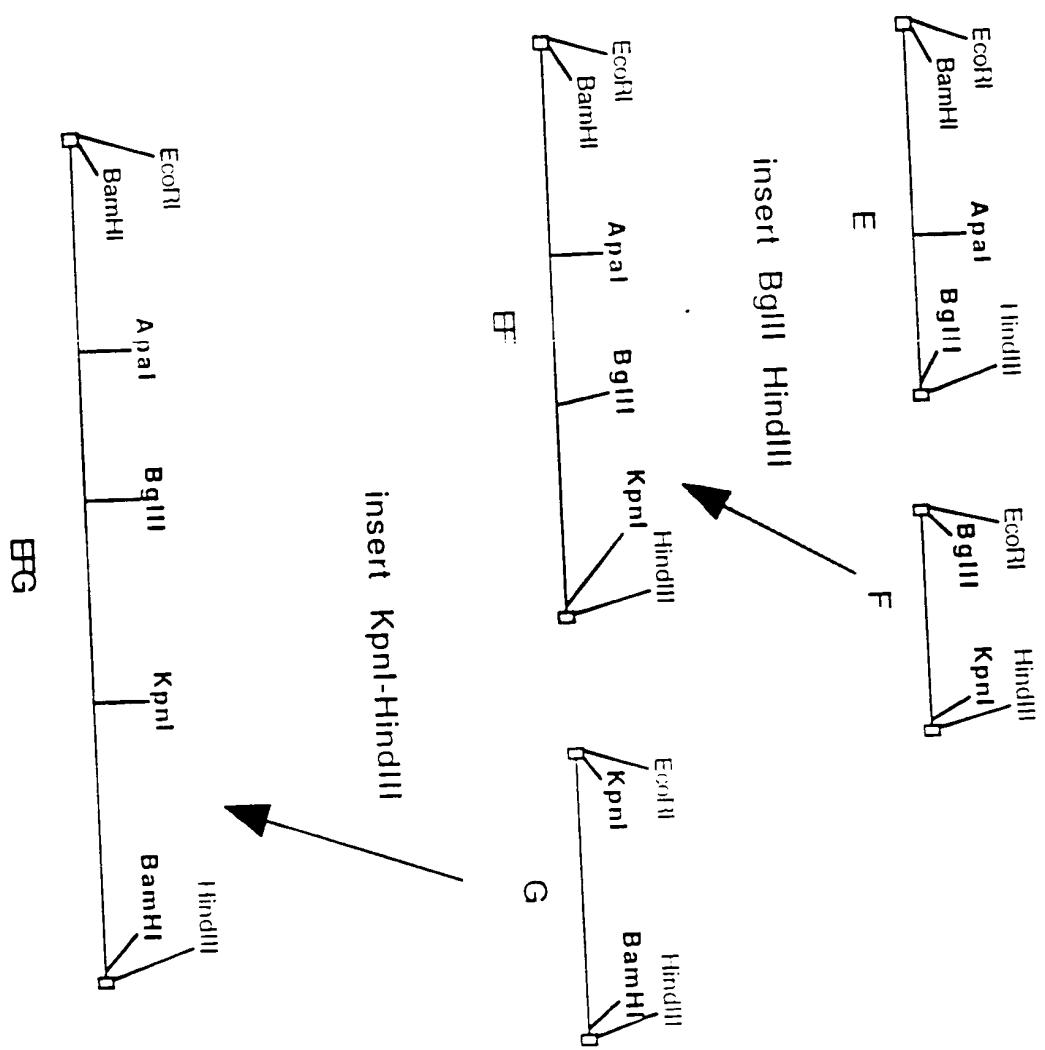
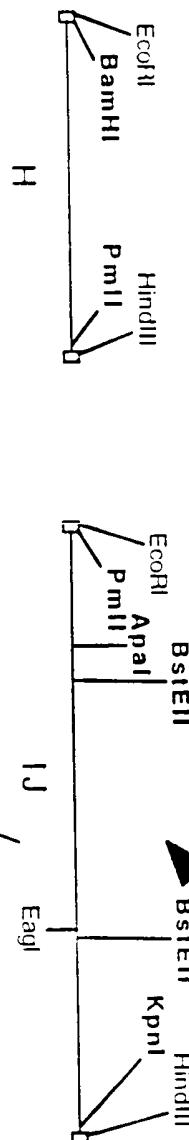
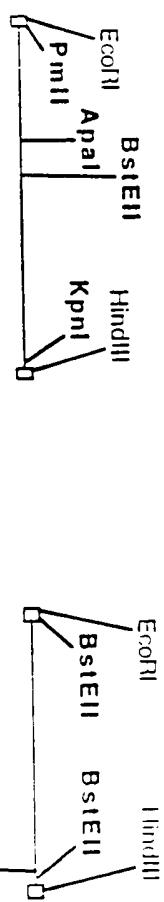


FIG. 6 (2 of 5)

insert BstEII - BstEII, map w Eagl



insert Pml - HindIII

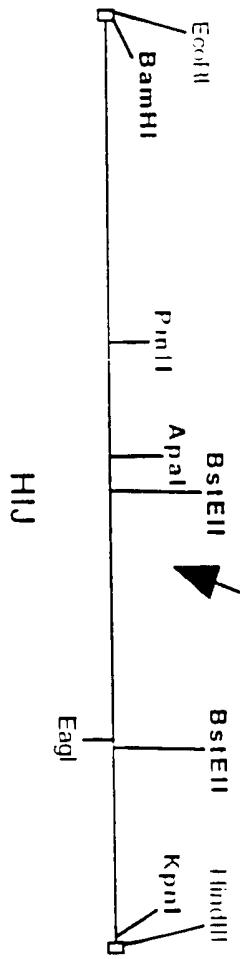


FIG. 6 (3 of 5)

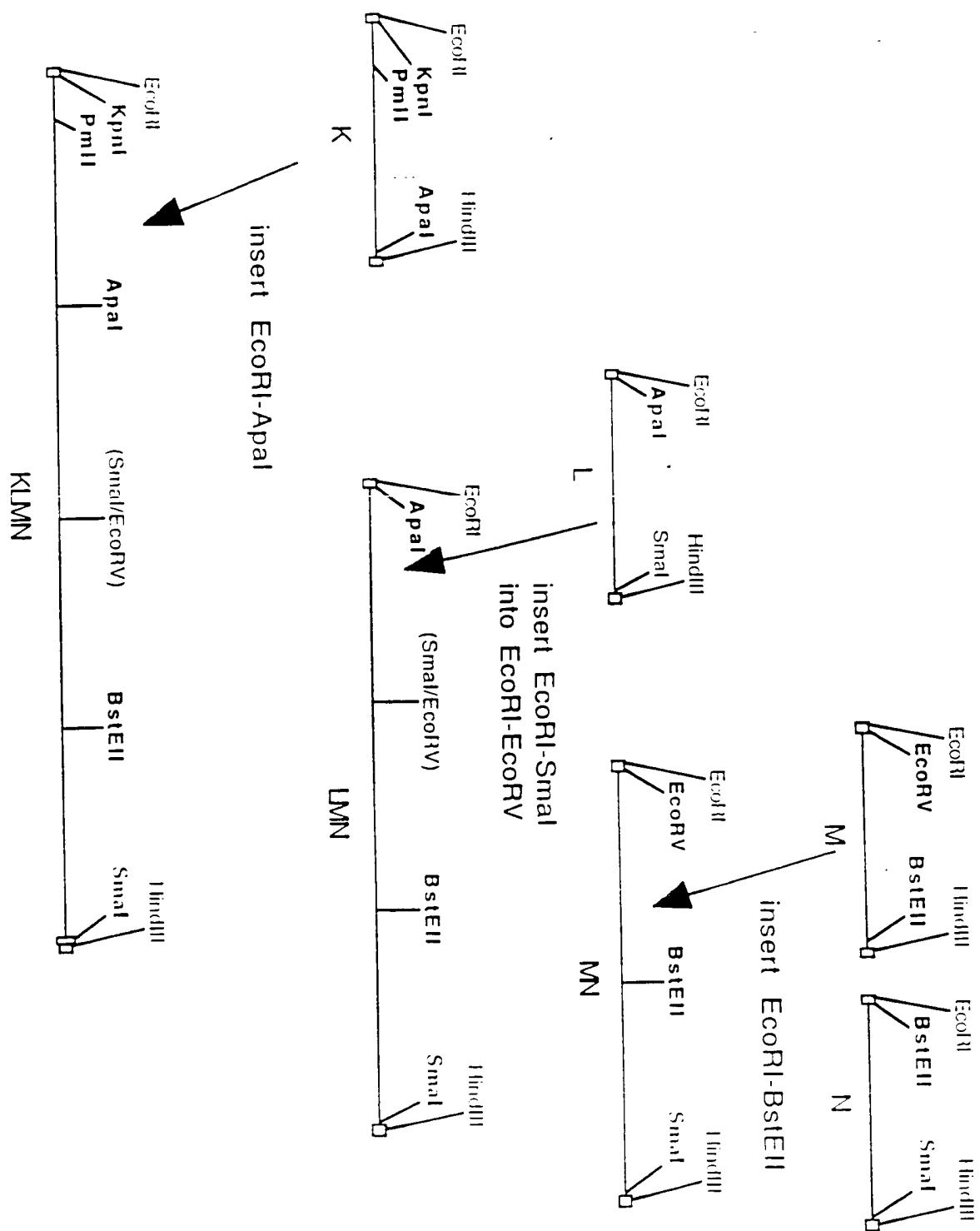


FIG. 6 (4 of 5)

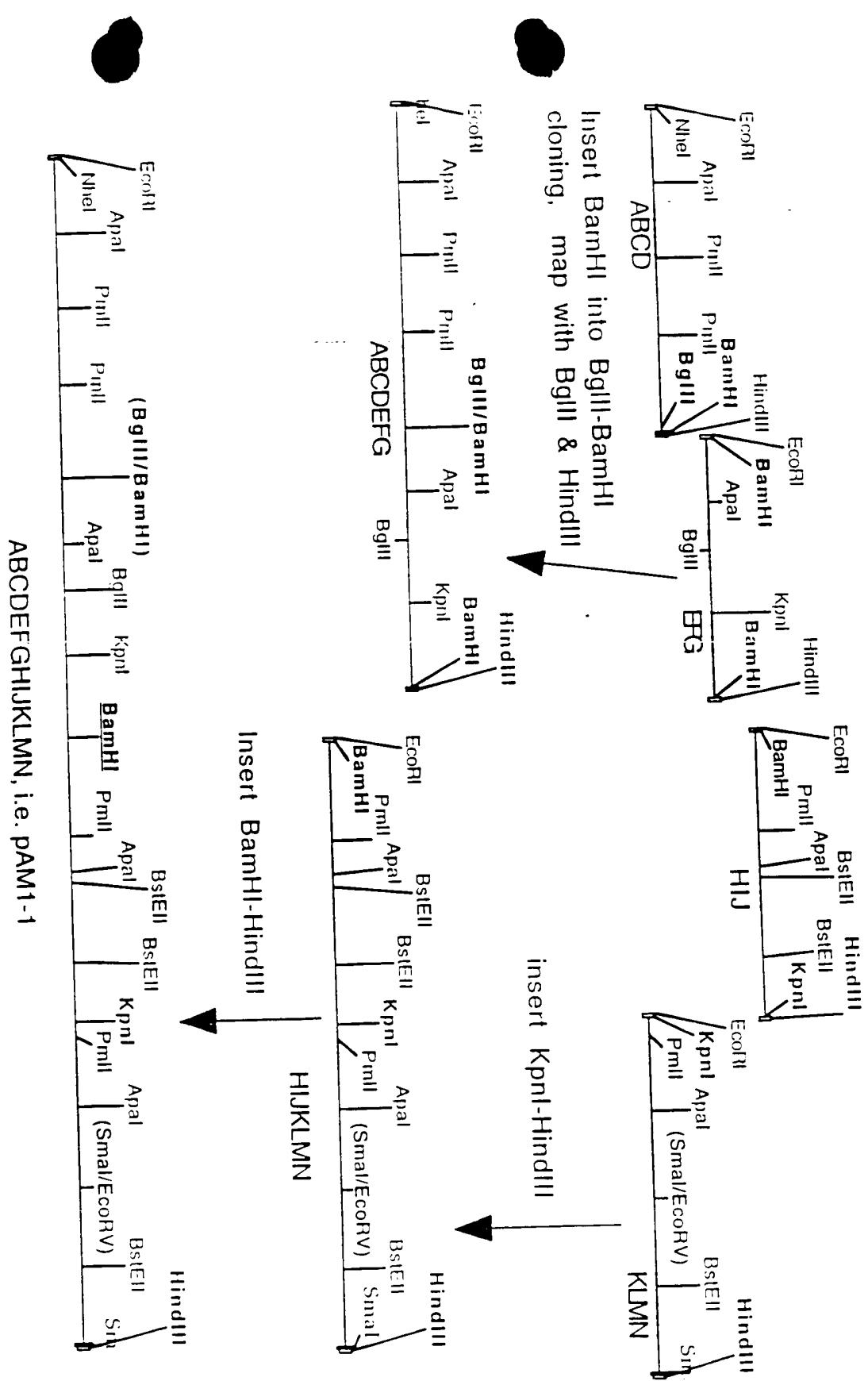


FIG. 6 (5 of 5)

EcoRI NheI

1 TAGAATTCTGTAGGCTAGCATGCCAGATCCAGCTGAGCACCTGCTTCTTCTGTGCCCTGCTGCCCTCTGCCCTC
1► MetGlnIleGluLeuSerThrCysPhePheLeuCysLeuLeuArgPheCysPhe
73 AGCGCCACCCCGCCGCTACTACCTGGCGCCCTGGAGCTGAGCTGGGACTACATGCCAGAGCGACCTGGCGAG
19► SerAlaThrArgArgTyrTyrLeuGlyAlaValGluLeuSerTrpAspTyrMetGlnSerAspLeuGlyGlu
145 CTGCCCCGTGGACGCCCGCTTCCCCCGCGTGCCTAAGAGCTTCCCTTCACACCAGCGTGGTGTACAAG
43► LeuProValAspAlaArgPheProProArgValProLysSerPheProPheAsnThrSerValValTyrLys
217 AAGACCCCTGTTCTGTGGAGGTTAACCGACCACCTGTTCAACATGCCAGCCCCCCCCCTGGATGGGCTG
67► LysThrLeuPheValGluPheThrAspHisLeuPheAsnIleAlaLysProArgProProTrpMetGlyLeu

Apal

289 CTGGGCCCCACCATCCAGGCCAGGTGTACGACACCGTGGTATCACCCCTGAAGAACATGGCCAGCCACCC
91► LeuGlyProThrIleGlnAlaGluValTyrAspThrValValIleThrLeuLysAsnMetAlaSerHisPro
361 CTGAGCCTGCACGCCGTGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCAGTACGACGACCAGACCAGC
115► ValSerLeuHisAlaValGlyValSerTyrTrpLysAlaSerGluGlyAlaGluTyrAspAspGlnThrSer
433 CAGCGCGAGAAGGAGGACGACAAGGTGTTCCCCGGCGCCACACCTACGTGGCAGGTGCTGAAGGAG
139► GlnArgGluLysGluAspAspLysValPheProGlyGlySerHisThrTyrValTrpGlnValLeuLysGlu

MscI

505 AACGGCCCCATGGCCAGCGACCCCTGTGCCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGAC
163► AsnGlyProMetAlaSerAspProLeuCysLeuThrTyrSerTyrLeuSerHisValAspLeuValLysAsp

MscI

577 CTGAACAGCGGCCTGATCGCGCCCTGCTGGTGTGCCCGAGGGCAGCCTGCCAAGGAGAACCCAGACC
187► LeuAsnSerGlyLeuIleGlyAlaLeuLeuValCysArgGluGlySerLeuAlaLysGluLysThrGlnThr
649 CTGCACAAGTTCATCCTGCTGTTGCCGTGTCGACGAGGGCAAGAGGCTGGCACAGCGAGACCAAGAACAGC
211► LeuHisLysPheIleLeuLeuPheAlaValPheAspGluGlyLysSerTrpHisSerGluThrLysAsnSer
721 CTGATGCAGGACCGCGACGCCAGGCCCGCCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAAC
235► LeuMetGlnAspArgAspAlaAlaSerAlaArgAlaTrpProLysMetHisThrValAsnGlyTyrValAsn

PmII

793 CGCAGCCTGCCCGGCCCTGATCGGCTGCCACCGCAAGAGCGTGTACTGGCACGTGATGGCATGGCACCC
259► ArgSerLeuProGlyLeuIleGlyCysHisArgLysSerValTyrTrpHisValIleGlyMetGlyThrThr
865 CCCGAGGTGCACAGCATCTCCTGGAGGGCCACACCTTCCTGGTGCACACCAGGCCAGGCTGGAG
283► ProGluValHisSerIlePheLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGlu
937 ATCAGCCCCATCACCTTCTGACCGCCCAGACCTGCTGATGGACCTGGCCAGTTCTGCTGTTCTGCCAC
307► IleSerProIleThrPheLeuThrAlaGlnThrLeuLeuMetAspLeuGlyGlnPheLeuLeuPheCysHis
1009 ATCAGCAGCCACCAGCACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCGAGGAGCCCCAGCTG
331► IleSerSerHisGlnHisAspGlyMetGluAlaTyrValLysValAspSerCysProGluGluProGlnLeu
1081 CGCATGAAGAACAAACGAGGAGGCCGAGGACTACGACGACCTGACCGACAGCGAGATGGACGTGGCGC
355► ArgMetLysAsnAsnGluAlaGluAspTyrAspAspAspLeuThrAspSerGluMetAspValValArg

(BglII/BamHI)

1153 TTGACGACGACAACAGCCCCAGCTTCATCCAGATCCGAGCGTGGCCAAGAACCCCCAAGACCTGGGTG
379► PheAspAspAspAsnSerProSerPheIleGlnIleArgSerValAlaLysLysHisProLysThrTrpVal
1225 CACTACATGCCGCCGAGGAGGGACTCGGACTACGCCCTGGTGTGCCCGACGACCGAGCTAC
403► HisTyrIleAlaAlaGluGluGluAspTrpAspTyrAlaProLeuValLeuAlaProAspAspArgSerTyr

EagI

1297 AAGAGCCAGTACCTGAACAAACGGCCCCAGCCATGGCCCAAGTACAAGAAGGTGCCCTCATGGCCTAC
427► LysSerGlnTyrLeuAsnAsnGlyProGlnArgIleGlyArgLysTyrLysValArgPheMetAlaTyr

Apal

1369 ACCGACGAGACCTCAAGACCCCGAGGCCATCCAGCACGAGAGCGGAGCGACCTGGCCCTGCTGTACGGC
451► ThrAspGluThrPheLysThrArgGluAlaIleGlnGluSerGlyIleLeuGlyProLeuLeuTyrGly

1441 CAGGTGGCCACACCCCTGCTGATCATCTTCAGAAACGAGGCCAGCCCCCCCTACAAACATCTACCCCCACGGC
1475 ▶ GluValGlyAspThrLeuLeuIleIlePheLysAsnGlnAlaSerArgProTyrAsnIleTyrProHisGly
1513 ATCACCCGACGTGCGCCCCCTGATCACGGCCCCCTGCCCCAGGGCGTGAAGCCTGAGGACTTCCCCATC
1549 ▶ IleThrAspValArgProLeuTyrSerArgArgLeuProLysGlyValLysHisLeuLysAspPheProIle

BglII

1585 CTGCCCGCGAGATCTTCAGTACAACTGGACCGTGACCGCTGGAGGACGGCCCCACCAAGAGGCCACCCCGC
1623 ▶ LeuProGlyGlulIlePheLysTyrLysTrpThrValThrValGluAspGlyProThrLysSerAspProArg
1657 TGCCTGACCCGCTACTACAGCAGCTCGTGAACATGGAGCGCGACCTGGCCAGCGCCCTGATCGGCCCCCTG
1694 ▶ CysLeuThrArgTyrTyrSerSerPheValAsnMetGluArgAspLeuAlaSerGlyLeuIleGlyProLeu
1729 CTGATCTGCTACAAGGAGAGCGTGGACCAGCGCCGAAACAGATCATGAGCGACAAGCGCACGTGATCTG
1767 ▶ LeuIleCysTyrLysGluSerValAspGlnArgGlyAsnGlnIleMetSerAspLysArgAsnValIleLeu

KpnI

1801 TTCAAGCGTGTTCGACGAGAACCGCAGCTGGTACCTGACCCAGAACATCCAGCGCTTCCTGCCAACCCCGCC
1839 ▶ PheSerValPheAspGluAsnArgSerTrpTyrLeuThrGluAsnIleGlnArgPheLeuProAsnProAla
1873 CGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGCTACGTGTTGAC
1919 ▶ GlyValGlnLeuGluAspProGluPheGlnAlaSerAsnIleMetHisSerIleAsnGlyTyrValPheAsp
1945 AGCCTGCAGCTGAGCGTGTGCCTGACAGGAGGTGGCTACTGGTACATCCTGAGCATGGCCAGACCGAC
1983 ▶ SerLeuGlnLeuSerValCysLeuHisGluValAlaTyrTyrIleLeuSerIleGlyAlaGlnThrAsp
2017 TTCTCTGAGCGTGTTCAGCGGCTACACCTCAAGCACAAGATGGTGTACAGGACACCTGACCCCTGTTTC
2057 ▶ PheLeuSerValPhePheSerGlyTyrThrPheLysHisLysMetValTyrGluAspThrLeuThrLeuPhe

BamHI

2089 CCCTTCAGCGCGAGACCGTGTTCATGAGCATGGAGAACCCCGGCCGTGGATCCTGGCTGCCACAACAGC
2127 ▶ ProPheSerGlyGluThrValPheMetSerMetGluAsnProGlyLeuTrpIleLeuGlyCysHisAsnSer
2161 GACTTCCGCAACCGCGGCCATGACCGCCCTGCTGAAGGTGAGCAGCTGCAGACAAGAACACCGCGACTACTAC
2200 ▶ AspPheArgAsnArgGlyMetThrAlaLeuLeuLysValSerSerCysAspLysAsnThrGlyAspTyrTyr
2233 GAGGACAGCTACGAGGGACATCAGCGCCTACCTGCTGAGCAAGAACACGCCATCGAGCCCCCTGGAGGAG
2270 ▶ GluAspSerTyrGluAspIleSerAlaTyrLeuLeuSerLysAsnAlaIleGluProArgLeuGluGlu

BstXI

2305 ATCACCCGACCCACCTGAGAGCGACCAGGAGGAGATGACTACGACGACACCATCAGCGTGGAGATGAAG
2343 ▶ IleThrArgThrThrLeuGlnSerAspGlnGluIleAspTyrAspAspThrIleSerValGluMetLys
2377 HAGGAGGACTTCGACATCTACGACGGAGAACAGAGCCCCCGAGCTTCCAGAAGAAGACCCCGCAG
2415 ▶ LysGluAspPheAspIleTyrAspGluAspGluAsnGlnSerProArgSerPheGlnLysIleTyrArgHis

PmlI

2449 TACTTCATGCCGCCGTGGAGCGCCGTGGACTACGGCATGAGCAGGCCACGTGCTGCCAACCGC
2487 ▶ TyrPheIleAlaAlaValGluArgLeuTrpAspTyrGlyMetSerSerProHisValLeuArgAsnArg
2521 CCCAGAGCGCCAGCGTCCCCAGTTCAAGAAGGTGGTCCAGGAGTTCACCGACGGCAGCTTCACCCAG
2559 ▶ AlaGlnSerGlySerValProGlnPheLysLysValValPheGlnGluPheThrAspGlySerPheThrGln

Apal

2593 CCCCTGTACCGCGGGAGCTGAACGAGCACCTGGGCCTGCTGGCCCCCTACATCCGGCCCCAGGTGAGGAC
2630 ▶ ProLeuTyrArgGlyGluLeuAsnGluHisLeuGlyLeuLeuGlyProTyrIleArgAlaGluValGluAsp

BstEII

2665 AACATCATGGTGACCTTCCGAAACCGAGGCCAGGCCACCTACAGCTTCTACAGCAGCCTGATCAGCTACGAG
2703 ▶ AsnIleMetValThrPheArgAsnGlnAlaSerArgProTyrSerPheTyrSerSerLeuIleSerTyrGlu
2737 GAGGACCAGCGCCAGGGCGCCAGGCCGGAAAGAACTTCGTGAAGCCACGAGACCAAGACCTACTCTGG
2775 ▶ GluAspGlnArgGlnGlyAlaGluProArgLysAsnPheValLysProAsnGluThrLysThrTyrPheTyr
2809 HAGGTGCAGCACCACATGGCCCCACCGAGGACCAAGTTCGACTGCAAGGGCTGGCCTACTTCAGCGACGTG

3381 CACCTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACCCACACCCCTGAAACCCC
3555► AspLeuGluLysAspValHisSerGlyLeuIleGlyProLeuLeuValCysHisThrAsnThrLeuAsnPro

EagI BstEII

2953 GCCCCACGGCCGCCAGGTGACCGCTGAGGAGTTGGCCCTCTTCTTCACCATCTTCGACGAGACCAAGAGCTGG
3079► AlaHisGlyArgGlnValThrValGlnGluPheAlaLeuPhePheThrIlePheAspGluThrLysSerTrp
3025 TACCTCACCGAGAACATGGAGCGCAACTGCCGCCCCCTGCAACATCCAGATGGAGGACCCACCTCAAG
1003► TyrPheThrGluAsnMetGluArgAsnCysArgAlaProCysAsnIleGlnMetGluAspProThrPheLys
3097 GAGAACTACCGCTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGCCCTGGTATGGCCCAGGAC
1027► GluAsnTyrArgPheHisAlaIleAsnGlyTyrIleMetAspThrLeuProGlyLeuValMetAlaGlnAsp

PmlI

3169 CAGCGCATCCGCTGGTACCTGAGCATGGCAGCAACGAGAACATCCACAGCATCCACTTCAGCGGCCAC
1051► GlnArgIleArgTrpTyrLeuLeuSerMetGlySerAsnGluAsnIleHisSerIleHisPheSerGlyHis
3241 GTGTTCACCGTGCAGCAAGAAGGAGGAGTACAAGATGGCCCTGTACAAACCTGTACCCCCGGCGTGTGAGACC
1075► ValPheThrValArgLysLysGluGluTyrLysMetAlaLeuTyrAsnLeuTyrProGlyValPheGluThr
3313 GTGGAGATGCTGCCAGCAAGGCCGATCTGGCGCTGGAGTGCCTGATGGCGAGCACCTGCACGCCGGC
1099► ValGluMetLeuProSerLysAlaGlyIleTrpArgValGluCysLeuIleGlyGluHisLeuHisAlaGly
3385 ATGAGCACCCCTTCCCTGGTACAGCAACAAGTGCCAGACCCCCCTGGCATGGCCAGCGGCCACATCCGC
1123► MetSerThrLeuPheLeuValTyrSerAsnLysCysGlnThrProLeuGlyMetAlaSerGlyHisIleArg

Apal

3457 GACTTCCAGATCACCGCCAGCGGCCAGTACGCCAGTGGCCCCAACGCTGGCCCGCTGCACTACAGCGGC
1147► AspPheGlnIleThrAlaSerGlyGlnTyrGlyGlnTrpAlaProLysLeuAlaArgLeuHisTyrSerGly
3529 AGCATCAACGCCCTGGAGCACCAAGGAGCCCTCAGCTGGATCAAGGTGGACCTGCTGGCCCCATGATCATC
1171► SerIleAsnAlaTrpSerThrLysGluProPheSerTrpIleLysValAspLeuLeuAlaProMetIleIle
3601 CACGGCATCAAGACCCAGGGCGCCCGCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATGTAC
1195► HisGlyIleLysThrGlnGlyAlaArgGlnLysPheSerSerLeuTyrIleSerGlnPheIleIleMetTyr
3673 AGCCTGGACGGCAAGAAGTGGCAGACCTACCGCGAACAGCACCGGCACCCGTATGGTCTTCGGCAAC
1219► SerLeuAspGlyLysLysTrpGlnThrTyrArgGlyAsnSerThrGlyThrLeuMetValPhePheGlyAsn

(SmaI/EcoRV)

3745 GTGGACAGCAGCGGCATCAAGCACAAACATCTCAACCCCCCATCATGCCGCTACATCCGCCTGCACCCC
1243► ValAspSerSerGlyIleLysHisAsnIlePheAsnProProIleIleAlaArgTyrIleArgLeuHisPro
3817 ACCCACTACAGCATCCCCAGCACCCTGCGATGGAGCTGATGGGCTGCGACCTGAAAGCTGCAGCATGCC
1267► ThrHisTyrSerIleArgSerThrLeuArgMetGlnLeuMetGlyCysAspLeuAsnSerCysSerMetPro
3889 CTGGGCATGGAGAGCAAGGCCATAGCGACGCCAGATCACCGCCAGCAGCTACTTCACCAACATGTTGCC
1291► LeuGlyMetGluSerLysAlaIleSerAspAlaGlnIleThrAlaSerSerTyrPheThrAsnMetPheAla
3961 ACCTGGAGCCCCAGCAAGGCCGCCTGCACCTGCAGGGCCAGCACGCCCTGGCGCCCCAGGTGAACAAAC
1315► ThrTrpSerProSerLysAlaArgLeuHisLeuGlnGlyArgSerAsnAlaTrpArgProGlnValAsnAsn

BstEII

4033 CCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGGACCATGAAGGTGACCGCGTGACCACCCAGGGCGTGAAG
1339► ProLysGluTrpLeuGlnValAspPheGlnLysThrMetLysValThrGlyValThrThrGlnGlyValLys
4105 AGCCTGCTGACCAGCATGTACGTGAGGAGTTCCCTGATCAGCAGCAGGCCAGGACGGCCACCAAGTGGACCTG
1363► SerLeuLeuThrSerMetTyrValLysGluPheLeuIleSerSerGlnAspGlyHisGlnTrpThrLeu
4177 TTCTTCCAGAACGGCAAGGTGAAGGTGTTCCAGGGCAACCAGGGACAGCTTCACCCCCGTGGTGAACAGCCTG
1387► PhePheGlnAsnGlyLysValLysValPheGlnGlyAsnGlnAspSerPheThrProValValAsnSerLeu
4249 GACCCCCCCCCTGCTCACCCCTACCTGCGATCCACCCCCAGAGCTGGTGCACCAAGATGCCCTGGCGATG
1411► AspProProLeuLeuThrArgPheLeuArgIleHisProGlnSerTrpValHisGlnIleAlaLeuArgMet

SmaI HindIII

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BRIEF HISTORY

GCCTTGAGGAGGATCGACTTACGACGCCATCAGGCTGGAACTTAC
GGCTCTGCTCTCTAGCTGATGCTGCTGTTGCTGTCCTTCGAATG

11001

FIG. 8

EcoRI NheI

1 TAGAAATTCTAGGCTAGCATGCAGATCGAGCTCAGCACCTCTTCTCTGCTGCTGCGCTCTGCTTC
1► MetGlnIleGluLeuSerThrCysPhePheLeuCysLeuLeuArgPheCysPhe
73 AGCGCCACCCGCCGCTACTACCTGGCGCCGCTGGAGCTCAGCTGGGACTACATGCAGAGCGACCTGGCGAG
19► serAlaThrArgArgTyrTyrLeuGlyAlaValGluLeuSerTrpAspTyrMetGlnSerAspLeuGlyGlu
145 CTGCCCCTGGACGCCGCTTCCCCCCCCCGTCCCCAGAGCTTCCCTTCAACACCAAGCGTGGTGTACAG
43► LeuProValAspAlaArgPheProProArgValProLysSerPheProPheAsnThrSerValValTyrLys
217 AGACCTGTTCTGGAGTTCAACCTGGCGCCAGCCTGGATGGGCCTG
67► LysThrLeuPheValGluPheThrAspHisLeuPheAsnIleAlaLysProArgProProTrpMetGlyLeu

Apal

289 CTGGGCCCCACCATCCAGGCCAGGGTGTACGACACCGTGGTATCACCTGAAGAACATGGCCAGCCACCC
91► LeuGlyProThrIleGlnAlaGluValTyrAspThrValValIleThrLeuLysAsnMetAlaSerHisPro
361 GTGAGCCTGCACGCCGTGGCGTGAGCTACTGGAAAGGCCAGCGAGGGCGCCAGTACGACGACCAGACCAGC
115► ValSerLeuHisAlaValGlyValSerTyrTrpLysAlaSerGluGlyAlaGluTyrAspAspGlnThrSer
433 CAGCGCGAGAAGGAGGACGACAAGGTGTTCCCCGGGGCAGCCACACCTACGTGTGGCAGGTGCTGAAGGAG
139► GlnArgGluLysGluAspAspLysValPheProGlyGlySerHisThrTyrValTrpGlnValLeuLysGlu

MscI

505 AACGGCCCCATGGCCAGCGACCCCTGTGCCTCACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGAC
163► AsnGlyProMetAlaSerAspProLeuCysLeuThrTyrSerTyrLeuSerHisValAspLeuValLysAsp

MscI

577 CTGAACAGCGGCCTGATCGGCCCTGCTGGTGTGCCCGAGGGCAGCCTGGCCAGGAGAACCCAGACC
187► LeuAsnSerGlyLeuIleGlyAlaLeuLeuValCysArgGluGlySerLeuAlaLysGluThrGlnThr
649 CTGCACAAAGTCATCCTGCTGTTGCGCGTGGACGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGC
211► LeuHisLysPheIleLeuLeuPheAlaValPheAspGluGlyLysSerTrpHisSerGluThrLysAsnSer
721 CTGATGCAGGACCGCGACGCCAGCGCCAGCCTGGCCAAAGATGCACACCGTGAACGGCTACGTGAAC
235► LeuMetGlnAspArgAspAlaAlaSerAlaArgAlaTrpProLysMetHisThrValAsnGlyTyrValAsn

PmlI

793 CGCAGCCTGCCCGCCTGATCGGCTGCCACCGCAAGAGCGTGTACTGGCACGTGATCGGATGGCACC
259► ArgSerLeuProGlyLeuIleGlyCysHisArgLysSerValTyrTrpHisValIleGlyMetGlyThrThr
365 CCCCGAGGTGCACAGGATCTTCTGGAGGGCCACCTTCTGGTGCAGCACCCACGCCAGGCCAGCCTGGAG
283► ProGluValHisSerIlePheLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGlu
337 ATCAGCCCCATCACCTTCTGACCCCGAGACCTGATGGACCTGGCCAGTTCTGCTGTTCTGCCAC
307► IleSerProIleThrPheLeuThrAlaGlnThrLeuLeuMetAspLeuGlyGlnPheLeuLeuPheCysHis
1009 ATCAGCAGGCCACCAGCACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCAGGGAGCCAGCTG
331► IleSerSerHisGlnHisAspGlyMetGluAlaTyrValLysValAspSerCysProGluGluProGlnLeu
1081 CGCATGAAGAACAGGAGGCCAGGACTACGACGACCTGACCGACAGCGAGATGGACGTGGCG
355► ArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspLeuThrAspSerGluMetAspValValArg

(BglII/BamHI)

1153 TTCGACGACGACAACAGCCCCAGCTTCATCCAGATCCGAGCGTGGCCAAGAACCCCCAACGACCTGGTG
379► PheAspAspAspAsnSerProSerPheIleGlnIleArgSerValAlaLysLysHisProLysThrTrpVal
1225 CACTACATGCCGCCAGGAGGAGGACTGGGACTACGCCCTGGCTGGCCCCACGACCCAGCTAC
403► HisTyrIleAlaAlaGluGluAspTrpAspTyrAlaProLeuValLeuAlaProAspAspArgSerTyr

EagI

1297 AGAGCCAGTACCTGAACAAACGGCCCCAGCCATGGCCCAAGTACAAGAACGGTGGCCTTCATGGCCTAC
427► LysSerGlnTyrLeuAsnAsnGlyProGlnArgIleGlyArgLysTyrLysValArgPheMetAlaTyr

Apal

1441 SAGGTGGGGGACACCCCTGCTGATCATCTTCAGAACCAAGCCAGCCGGCCCTACACATCTACCCCCACGGC
475▶ GluValGlyAspThrLeuLeuIlePheLysAsnGlnAlaSerArgProTyrAsnIleTyrProHisGly
1513 ATCACCCGACGTGCGGCCCCCTCTACAGCCGCCGCTGCCAGGGCCTGAAGCACCTGAAGGACTTCCCCATC
499▶ IleThrAspValArgProLeuTyrSerArgArgLeuProLysGlyValLysHisLeuLysAspPheProIle

BglII

1585 ATGCCCGGGGAGATCTTCAGTACAAGTGGACCGCTGACCGCTGGAGGACGGCCCCACCAAGAGCGACCCCCGC
523▶ LeuProGlyGluIlePheLysTyrLysTrpThrValThrValGluAspGlyProThrLysSerAspProArg
1657 TGCCTGACCCGCTACTACAGCAGCTTCGTGAACATGGAGCGCGACCTGGCCAGCGGCCCTGATCGGCCCCCTG
547▶ CysLeuThrArgTyrTyrSerSerPheValAsnMetGluArgAspLeuAlaSerGlyLeuIleGlyProLeu
1729 CTGATCTGCTACAAGGAGAGCGTGGACCAGCGCGCAACCAGATCATGAGCGACAAGCGAACGTGATCCTG
571▶ LeuIleCysTyrLysGluSerValAspGlnArgGlyAsnGlnIleMetSerAspLysArgAsnValIleLeu

KpnI

1801 TTCAAGCGTGTTCGACGAGAACCCAGCTGGTACCTGACCCAGAACATCCAGCGCTTCCTGCCAACCCGCC
595▶ PheSerValPheAspGluAsnArgSerTrpTyrLeuThrGluAsnIleGlnArgPheLeuProAsnProAla
1873 GGCCTGCAGCTGGAGGACCCCCAGTTCCAGGCCAGCAGCATCATGCCACAGCATCAACGGCTACGTGTTGAC
619▶ GlyValGlnLeuGluAspProGluPheGinAlaSerAsnIleMetHisSerIleAsnGlyTyrValPheAsp
1945 ACCCTCCAGCTGAGCGTGTCCATGCCAGGGTGGCTACTGGTACATCCTGAGCATTGGCGCCAGACCGAC
643▶ SerLeuGlnLeuSerValCysLeuHisGluValAlaTyrTrpTyrIleLeuSerIleGlyAlaGlnThrAsp
2017 TTCCCTGAGCGTGTCTTCAGCGGCTACACCTCAAGCACAGATGGTGTACGAGGACACCCCTGACCCCTGTC
667▶ PheLeuSerValPhePheSerGlyTyrThrPheLysHisLysMetValTyrGluAspThrLeuThrLeuPhe

BamHI

2089 CCCTTCAGCGGGCAGACCCGTGTTCATGAGCATGGAGAACCCCGGCCTGGATCCTGGGCTGCCAACACAGC
691▶ ProPheSerGlyGluThrValPheMetSerMetGluAsnProGlyLeuTrpIleLeuGlyCysHisAsnSer
2161 GACTTCCGCAACCGCGGCATGACCGCCCTGCTGAAGGTGAGCAGCTGCGACAAGAACACCGGGCAGTACTAC
715▶ AspPheArgAsnArgGlyMetThrAlaLeuLysValSerSerCysAspLysAsnThrGlyAspTyrTyr
2233 GAGGACAGCTACGAGGACATCAGCGCCATCCCTGCTGAGCAAGAACACGCCATCGAGCCCCCGCAGGCGCAGG
739▶ GluAspSerTyrGluAspIleSerAlaTyrLeuLeuSerLysAsnAsnAlaIleGluProArgArgArg

BstXI

2305 CGCGAGATCACCCGACCAACCTGAGAGCGACCAAGGAGGAGATGACTACGACGACACCATCAGCGTGGAG
763▶ ArgGluIleThrArgThrLeuGlnSerAspGlnGluGluIleAspTyrAspAspThrIleSerValGlu
2377 ATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAAGAGCCCCCGCAGCTTCCAGAAGAAC
787▶ MetLysLysGluAspPheAspIleTyrAspGluAspGluAsnGlnSerProArgSerPheGlnLysThr

PmlI

2449 CGCCACTACTCATGCCGCCGTGGAGCGCCTGGGGACTACGGCATGAGCAGCAGCCCCCACGTGCTGCGC
811▶ ArgHisTyrPheIleAlaAlaValGluArgLeuTrpAspTyrGlyMetSerSerSerProHisValLeuArg
2521 AACCGCGCCCAGAGCGGCAGCGTGCCTCAGTTCAAGAAGGTGGTGTCCAGGAGTTCACCGACGGCAGCTTC
835▶ AsnArgAlaGlnSerGlySerValProGlnPheLysValValPheGlnGluPheThrAspGlySerPhe

Apal

2593 ACCCAGCCCTGTACCGGGGAGCTAACGAGGACCTGGCCCTGGCCCTACATCCGGCCAGGGT
859▶ ThrGlnProLeuTyrArgGlyGluLeuAsnGluHisIleGlyLeuLeuGlyProTyrIleArgAlaGluVal

BstEII

2665 CAGGACACATCATGGTACCTCCGCCAACAGGCCAGCCGGCCCTACAGCTTCTACAGCAGCCCTGATCGC
383▶ GluAspAsnIleMetValThrPheArgAsnGlnAlaSerArgProTyrSerPheTyrSerSerLeuIleSer
2737 TACGAGGGAGGACCAGCGCCAGGGCGCCAGGCCAGGGCAAGAACCTCGTGAAGGCCACCGAGACCAAGACCTAC
907▶ TyrGluGluAspGlnArgGlnGlyAlaGluProArgLysAsnPheValLysProAsnGluThrLysThrTyr

3681 AACGTGGACCTGGAGAAGGACGTGCACAGCGGCCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCCTG
3655 ► AspValAspLeuGluLysAspValHisSerGlyLeuIleGlyProLeuLeuValCysHisThrAsnThrLeu

EagI BstEII

3693 AACCCCCCCCACGGCCGCCAGTGACCGCTGCAGGAGTTGCCCTGTTCTCACCATCTTCGACGAGACCCAG
3679 ► AsnProAlaHisGlyArgGlnValThrValGlnGluPheAlaLeuPhePheThrIlePheAspGluThrLys

3702 AGCTGGTACTTCACCGAGAACATGGAGGCCAACCTGCCCGCCCCCTGCAACATCCAGATGGAGGACCCCAC
3700 ► SerTrpTyrPheThrGluAsnMetGluArgAsnCysArgAlaProCysAsnIleGlnMetGluAspProThr

3709 TTCAAGGAGAACTACCGCTTCCACGCCATCAACGGCTACATCATGGACACCCCTGCCCGCTGGTATGGC
3707 ► PheLysGluAsnTyrArgPheHisAlaIleAsnGlyTyrIleMetAspThrLeuProGlyLeuValMetAla

KpnI

3716 CAGGACCAGCGCATCCGCTGGTACCTGCTGAGCATGGCAGCAACGAGAACATCCACGCATCCACTTCAGC
3701 ► GlnAspGlnArgIleArgTrpTyrLeuLeuSerMetGlySerAsnGluAsnIleHisSerIleHisPheSer

PmlI

3724 GGCCACGTGTTCACCGTGCAGAACAGGAGGAGTACAAGATGGCCCTGTAACACCTCTACCCCGCGTGTTC
3707 ► GlyHisValPheThrValArgLysGluGluTyrLysMetAlaLeuTyrAsnLeuTyrProGlyValPhe

3731 GAGACCGTGGAGATGCTGCCAGCAAGGCCGCATCTGGCGCGTGGAGTGCCTGATCGCGAGCACCTGCCAC

3739 ► GluThrValGluMetLeuProSerLysAlaGlyIleTrpArgValGluCysLeuIleGlyGluHisLeuHis

3745 GCGGCATGAGCACCCCTGTTCTGGTGTACAGCAACAGTGCAGACCCCCCTGGGATGGCCAGCGGCCAC

3743 ► AlaGlyMetSerThrLeuPheLeuValTyrSerAsnLysCysGlnThrProLeuGlyMetAlaSerGlyHis

Apal

3757 ATCCGGCAGTCCAGATCACCGCCAGCGGCCAGTACGGCCAGTGGCCCCAAAGCTGGCCGCTGCACATC
3741 ► IleArgAspPheGlnIleThrAlaSerGlyGlnTyrGlyGlnTrpAlaProLysLeuAlaArgLeuHisTyr

3759 AGCGGCAGCATCAACGCCTGGAGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCATG

3771 ► SerGlySerIleAsnAlaTrpSerThrLysGluProPheSerTrpIleLysValAspLeuLeuAlaProMet

3761 ATCATCCACGGCATCAAGAGCCCAGGGCGCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATC

3769 ► IleIleHisGlyIleLysThrGlnGlyAlaArgGlnLysPheSerSerLeuTyrIleSerGlnPheIleIle

3773 ATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGCGGCAACAGCACCGGCACCCGTATGGTGTCTC

3771 ► MetTyrSerLeuAspGlyLysTrpGlnThrTyrArgGlyAsnSerThrGlyThrLeuMetValPhePhe

(SmaI/EcoRV)

3785 GGCACACGTGGACAGCAGCGGCATCAAGCACACATCTCAACCCCCCATCATCGCCCGCTACATCCGCCTG

3763 ► GlyAsnValAspSerSerGlyIleLysHisAsnIlePheAsnProProIleIleAlaArgTyrIleArgLeu

3781 GACCCCCACCCACTACAGCATCCGAGCACCCCTGCCATGGAGCTGATGGCTGCCAGCTGAAACAGCTGCCAGC

3767 ► HisProThrHisTyrSerIleArgSerThrLeuArgMetGluLeuMetGlyCysAspLeuAsnSerCysSer

3789 ATGCCCTGGGCATGGAGAGCAAGGCCATAGCGACGCCAGATCACGCCAGCAGCTACTTCACCAACATG

3791 ► MetProLeuGlyMetGluSerLysAlaIleSerAspAlaGlnIleThrAlaSerSerTyrPheThrAsnMet

3796 TTGGCCACCTGGAGCCCCAGCAAGGCCGCCTGCACCTGCAGGGCCCCAGCAACGCCCTGGCGCCCCCAGGTG

3791 ► PheAlaThrTrpSerProSerLysAlaArgLeuHisLeuGlnGlyArgSerAsnAlaTrpArgProGlnVal

BstEII

3803 AACAAACCCCAAGGAGTGGCTCAGGTGGACTTCCAGAACAGACCATGAAGGTGACCGCGGTGACCAACCCAGGGC

3809 ► AsnAsnProLysGluTrpLeuGlnValAspPheGlnLysThrMetLysValThrGlyValThrThrGlnGly

3810 GTGAAGAGCCTGCTGACCAAGCATGTACGTGAAGGAGTTCCCTGATCAGCAGCAGCCAGGACGCCACCAAGTGG

3813 ► ValLysSerLeuLeuThrSerMetTyrValLysGluPheLeuIleSerSerGlnAspGlyHisGlnTrp

3817 ACCCTGTTCTTCCAGAACGGCAAGGTGAAGGTGTTCCAGGGCAACCAAGGACAGCAGCTTCACCCCGTGGTGAAC

3817 ► ThrLeuPhePheGlnAsnGlyLysValLysValPheGlnGlyAsnGlnAspSerPheThrProValValAsn

3824 AGCCTGGACCCCCCCCCTGCTGACCCGCTACCTGCCATCCACCCCCAGAGCTGGTGCACCAAGATGCCCTG

3829 ► SerLeuAspProProLeuLeuThrArgTyrLeuArgIleHisProGlnSerTrpValHisGlnIleAlaLeu

SmaI HindIII

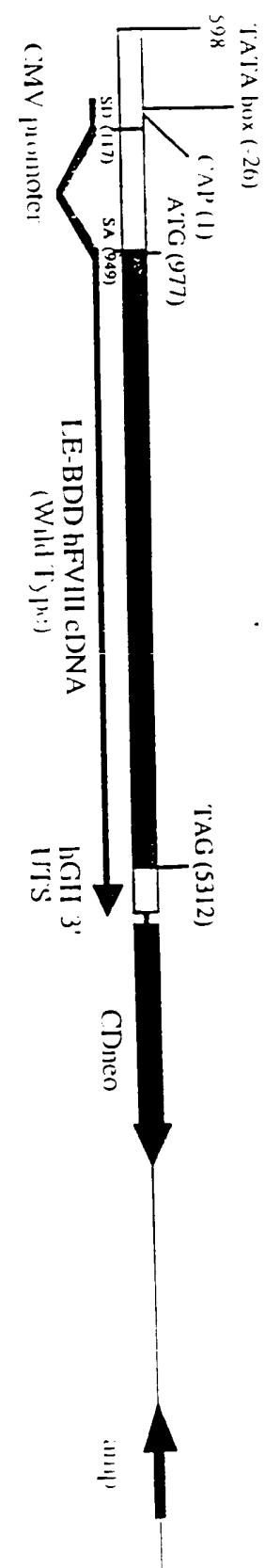


FIG. 10

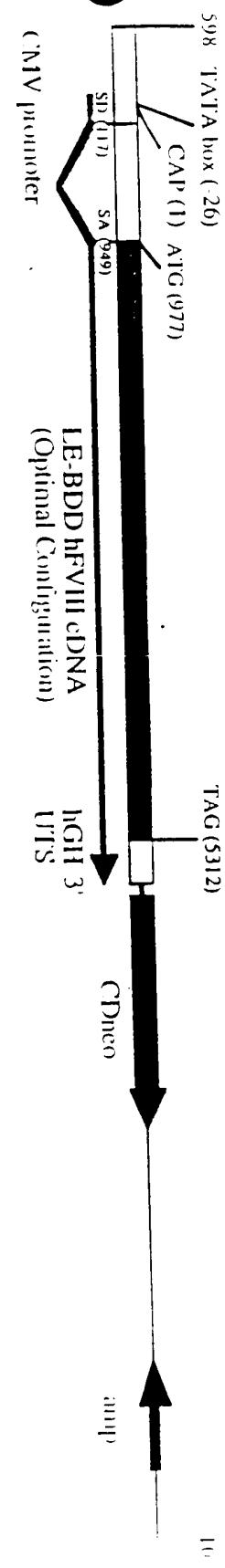


FIG. 11

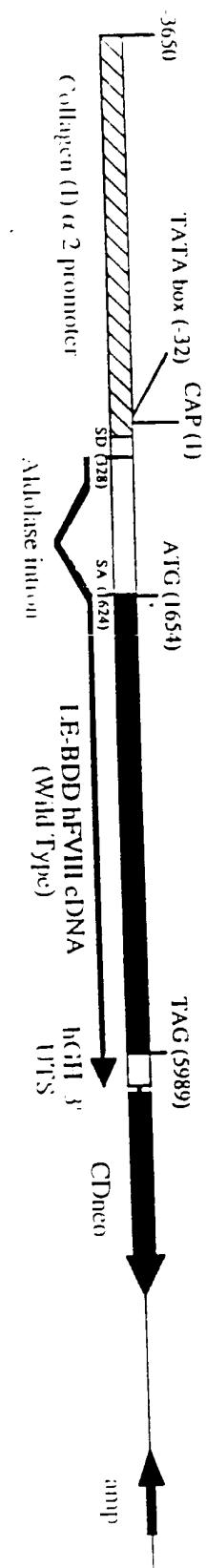


FIG. 12

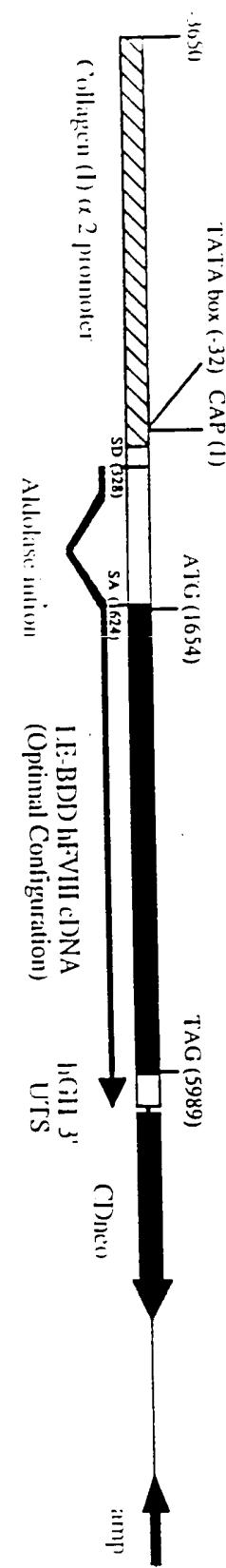


FIG. 13